REMARKS

The amendments and remarks presented here are believed to place the case in condition for allowance. None of the amendments made herein constitutes the addition of new matter. With this response, claims 1, 2, 4, 25-32, 39-42, and 44-62 are pending in the application.

Declaration

An executed Declaration of Dr. Jeffrey Michael Hammond is included in support of this response and is referred to as the Second Declaration. As the executed Second Declaration was provided via facsimile, for legibility purposes a second copy is provided that includes a figure in color for the convenience of the Examiner.

Information Disclosure Statement

A Second Supplemental Information Disclosure Statement accompanies this response.

The Amendments

Claims 1, 2, 31, and 39 have been amended to include a limitation specifying that the location of an insertion site for a heterologous DNA is in a right hand end of the porcine adenovirus genome, where the right hand end is defined as comprising from about 50 genomic map units to about 100 genomic map units. As is known in the art and addressed in Dr. Hammond's Second Declaration, referring to portions of genes in terms of arbitrary genomic map units is conventional in the art, all genomes being comprised of 100 map units. Support is found in original Claim 27 which discloses a "right hand end of the genome" and at page 13, lines 5-11. The latter reference distinguishes the "left end" and notes that "The genomes are orientated left to right."

Claim 27 is canceled. Claim 28 is amended regarding the precision of map units and for dependency in light of canceled claim 27. Claim 30 is amended regarding the precision of map units.

Rejections Under 35 USC 112, first paragraph

Written Description

Claims 1, 2, 4, 25-32, 39-42, 44 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The reasons of record, as set forth in the Office Action dated August 27, 2003, are as follows.

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a recombinant porcine adenoviral vector capable of expressing heterologous gene sequence. The specification has shown the insertion of heterologous sequences into the right hand region or E3 region of PAV 3. However, the claims are broadly drawn to include sites of insertion of heterologous DNA at any point in the adenovirus region including the E1 and E4 regions, which have not been sufficiently described in terms of their structure.
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> The 37 C.F .R. 1.132 Declaration of Jeffrey Hammond (Paper _No. 24) explained that applicants have constructed a major late promoter-leader sequence expression cassette which is includes sequences from the tri-partite leader sequences, these leader sequences are found spread over a kilo base region of the genome which differs from the human adenoviral genome. Because of this difference between human and porcine adenovirus sequences, the structure of the human adenovirus does not provide sufficient structural information to determine the function of porcine adenovirus. The declaration indicates that it is necessary to have an understanding of the structure of the porcine adenovirus in order to determine the major late promoter and the requisite leader sequences. This sequences information was not available in the art at the time of filing. Applicants in their instant specification have provided the necessary structural information to produce a major late promoter (MLP) cassette which they used for the homologues recombination in order to produce porcine adenoviral vector with a heterologous sequence inserted. The declaration goes onto explain that homologues recombination for porcine adenoviruses, unexpectedly requires the use of a primary pig kidney cell line although the virus grows well in PK15 cells. Because the cells grow well in the PK15 cells, the need to process the constructs in a primary pig kidney cell is not obvious. To summarize the declaration clearly sets out that (1) knowledge of the structure of the tri-partite leader and major late promoter is required (2) and the requirement for processing through primary pig kidney cells.
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> To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor in the specification is a partial structure in the form of the major late promoter and tripartite leader sequence. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus which reads on all porcine adenoviruses discovered and those yet to be discovered. Furthermore, at the time of filing there was no information in the art or in the specification regarding sequences of complete P A V genomes, this information is necessary to insert heterologous genes into regions other than the PAV E3 or right hand genome region disclosed. In order for homologous recombination to take place the key requirement is the alignment of homologous sequences in two DNA molecules, in the is case these sequences will be present in the wild type virus and they will also need to be present in the shuttle vector providing the

heterologous sequence of interest which is to be inserted into the porcine adenovirus. To create the appropriate shuttle vector requires structural knowledge [of] the region into which the heterologous sequence is to be inserted.

Vas-Cath Inc. v. Mahurkar, 19U5PQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus porcine adenovirus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.
A definition by function alone "does not suffice, to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lily, 119 F.3 at 1568,43 USPQ2d at 1406.

> It means little to "invent" a method if one does; not have possession of a substance that is essential to practicing that method. Without that substance, the claimed invention is more theoretical than real; it is, as defendants argue, akin to "inventing" a cure for cancer by utilizing a substance that attacks and destroys cancer cells while leaving healthy cells alone. Without possession of such a substance, such a cure is illusory, and there is no meaningful possessions of the method. (see 00-CY-6161, March 5th 2003 decision, United States District Court Western District of New York, Judge Larimer).

Based on the requirement for the structural knowledge regarding the insertion points in the porcine adenoviral vector, the instant invention does not provide a sufficient written description for insertion into regions other than the E3 or right hand genome region or for the use of another promoter cassette. Therefore, the instant specification does not provide sufficient written description for the breadth of the claimed invention.

This rejection is respectfully traversed.

Applicants address the issue of whether the written description requirement is satisfied in connection with the use of primary pig kidney cells. Applicants respectfully point out that in the Preferred Embodiments section of the application at page 15, lines 28-29, the application states, "The DNA mix was transfected into preferably primary pig kidney cells by standard calcium chloride precipitation techniques." Dr. Hammond's First Declaration discussed the fact that the art-known PK15 cells were ineffective in the generation of recombinants, and this difficulty supported Applicant's argument that the invention was not obvious. This did not imply, however, that the selection and use of

primary pig kidney cells as disclosed was the only possible way to obtain results, efficiently or inefficiently. The selection was simply a preferred embodiment. It is well settled that that a claim need not be limited to a preferred embodiment (Lampi Corp. v. American Power Products, Inc., 228 F.3d 1365, 1378 (Fed. Cir. 2000). Applicants demonstrate possession of the claimed invention at the time the application was filed and otherwise satisfy the written description requirement. Therefore, it is not necessary to limit the claimed invention to the use of primary pig kidney cells.

Applicants address the issue of whether the written description requirement is satisfied in connection with the sequence or structural information of the porcine adenovirus genome. Applicants note that at or before the time of filing, some such information was disclosed in the instant application and that other such information was available elsewhere. Regarding the latter, a Declaration under 37 CFR 132 of Dr. Jeffrey Michael Hammond is presented herewith providing evidence in support of a determination that certain sequence or structural information was available as public knowledge.

As an overview, Applicants suggest that the claims as currently amended are fully supported and comply with the written description requirement. The amended claims have a limitation of insertion of heterologous DNA in a right hand end of the porcine adenovirus genome, where the right hand end is defined as from about 50 to about 100 map units. More specifically, the information in the specification together with information in the art available at the priority date provides adequate structural information of the PAV genome to allow the skilled person to insert heterologous sequences into the right hand end as defined herein.

In the instant application, the specification provides specific examples of insertion of a heterologous sequence into the terminal right hand end of the genome between map units 97 to 99.5 and in the E3 region of the genome between map units 81 and 84 (see page 7, lines 1-3, et al.) Both insertion sites are within the right hand end as defined herein.

The specification also provides sequence information of the E4 region which is within the right hand end as defined. The sequence information of Figure 4 includes the Inverted Terminal Repeat, a non-coding region containing the E4 start of transcription site and a portion of the E4 coding sequence including the E4 region Open Reading Frame A (ORF-A). This region corresponds to approximately 91 to 99 map units. This sequence information could be used to insert heterologous sequences into regions other than the regions disclosed in the examples. To clarify the regions of the genome identified by the Applicants, Figure A1 is included in the Second Declaration of Dr. Hammond.

Furthermore, the specification provides restriction enzyme maps, using multiple enzymes, of the entire PAV 3 genome (Figure 1). This information would allow the skilled person to construct an expression cassette with unique restriction enzyme sites flanking the cassette, thus describing and enabling insertion in the PAV genome and in particular the right hand end as defined.

Outside the instant application, other information was available as public knowledge of the structure or sequence of porcine adenovirus. To summarize certain material in the Second Declaration of Dr. Hammond, partial sequence information was published as early as 1996 approximating to map units 50 to 55, 55 to 65, and 72 to 85 (see Second Declaration and accompanying Second Supplemental Information Disclosure Statement). Upon including Applicant's disclosure corresponding to map units 81 to 84 and 97 to 99.5, Applicant clearly demonstrates satisfaction of the written description requirement of the invention as claimed for insertions in the right hand end comprising map units 50 to 100.

Since Applicants provide sufficient distinguishing characteristics of the genus of porcine adenoviruses, Applicants are entitled to claim the entire genus. The Office Action states that in order to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. Factors include complete/partial structure,

functional characteristics and physical properties. The Office Action states that the only factor provided in the specification is a partial structure in the form of the major late promoter and tripartite leader sequence. Applicants respectfully assert that this is incorrect and note the discussion above which demonstrates that multiple factors are provided. The specification provides a complete restriction enzyme map of the entire PAV3 genome together with sequence information relating to the E3 and E4 regions of the genome including the major late promoter and tripartite leader sequences. Further, the specification provides functional and physical information about PAV 3 and other PAV serotypes.

As noted in Dr. Hammond's Second Declaration, all porcine adenoviruses are classified in the genus Mastadenoviridae, and there was a strong expectation by the skilled person at the priority date that the genome structure would be conserved across the genus. Consistent with such expectation, information in the reference database at *http://www.ncbi.nlm.nih.gov/ICTVdb/Ictv/index.htm* (the official site of the international classification system for viruses) establishes that there is strict conservation of genome organisation among the various serotypes of the PAV. Thus this information verifies that the expectations of the skilled person at the priority date were correct and that the description of PAV 3 disclosed in the specification could be applied to all serotypes of the genus.

Regarding the assertion that the specification does not provide sufficient description for the use of another promoter cassette, Applicants respectfully respond that adequate written description is indeed provided. The sequence information of the major late promoter, tripartite leader sequence and the E4 region disclosed in the specification would allow the skilled person to construct other expression cassettes. The specification disclosed the key elements of the cassette, and as known to those skilled in the art, these elements could be used with other flanking sequences to construct cassettes for insertion in other regions of the PAV genome other than those shown. Moreover, as already discussed (see above and Dr. Hammond's Second

Declaration), there was partial sequence information available in the art at the priority date which could be used for flanking sequences for insertion cassettes.

The Office Action states that a definition by function alone is insufficient to describe a coding sequence because it is only an indication of what the gene does, rather than what it is. Here, Applicants have provided significant structural information in the instant application and have noted several sources of public knowledge in the art also relating to partial structures. Thus Applicants go well beyond defining the subject matter by function alone.

The Office Action also cites the University of Rochester decision, now upheld at the appellate level, where a patent was invalidated on grounds of lack of written description. See University of Rochester v. G.D. Searle et al. (Fed. Cir. 2004; February 13 decision) (no citation available). There, a therapeutic method was claimed that required the use of a compound as a selective inhibitor of a particular enzyme, but not a single compound was disclosed. Thus the Rochester inventors could not demonstrate possession of even one such compound. Nor could the inventors show knowledge "of any such compound at the time their patent application was filed." Univ. of Rochester at page 2, (Fed. Cir. 2004; slip opinion). The Rochester patent:

> does not provide any guidance that would steer the skilled practitioner toward compounds that can be used to carry out the claimed methods—an essential element of every claim of that patent—and has not provided evidence that any such compounds were otherwise within the knowledge of a person of ordinary skill in the art at the relevant time. Id. at 21.

The facts of that case are inapposite to the present situation. Here, for example, Applicants claim recombinant porcine adenoviruses and recombinant vectors, and provide substantial and relevant disclosure of structures and sequences that correspond to just such compositions and related methods. Moreover, Applicants teach specific examples and preferred embodiments precisely with respect to the claimed subject matter; the Applicants have described what the material **is**. Others skilled in the art can clearly recognize what is claimed from what is described. Applicant's disclosure and the

state of public knowledge simply cannot be compared to a mere wish or plan to cure cancer. As disclosed in the specification and as stated in the interview on June 11, 2003 and the related Supplemental Amendment of June 12, 2003, Applicant's contribution to the art, in marked contrast to the situation in the cited Rochester decision, has directly resulted in the meaningful practice of the invention.

In the context of written description, the Court of Appeals of the Federal Circuit has spoken further:

> The disclosure as originally filed does not, however, have to provide in haec verba support for the claimed subject matter at issue. See Fujikawa v. Wattanasin, 93 F.3d 1559, 1570 (Fed. Cir. 1996) (cited in Cordis Corp. v. Medtronic AVE Inc., 67 USPQ2d 1876 (Fed. Cir. 2003)).
>
> As our case law makes clear, however, "[a]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention." Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1344 (Fed. Cir. 2001). "A specification may, within the meaning of 35 U.S.C. § 112 para. 1, contain a written description of a broadly claimed invention without describing all species that [the] claim encompasses." Utter v. Hiraga, 845 F.2d 993, 998 (Fed. Cir. 1988) (cited in Cordis Corp. v. Medtronic AVE Inc., 67 USPQ2d 1876 (Fed. Cir. 2003)).
>
> [i]t is a familiar principle of patent law that a claim need not be limited to a preferred embodiment (Lampi Corp. v. American Power Products, Inc., 228 F.3d 1365, 1378 (Fed. Cir. 2000) (cited in Cordis Corp. v. Medtronic AVE Inc., 67 USPQ2d 1876 (Fed. Cir. 2003)).

In that perspective, Applicants note that the specification describes PAV3 as a preferred candidate for vaccine vectors, and the examples provided relate to the use of PAV 3 for the construction of recombinant vectors. PAV3 is illustrative only and the examples provided should not limit the scope of protection.

Enablement

Claims 1,2,4,25-32,39-42,44 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention. The reasons of record, as set forth in the Office Action dated August 27, 2003, are as follows.

> The claims are drawn to a recombinant porcine adenoviral vector capable of expressing a heterologous gene sequence. The specification has shown the insertion of heterologous sequences into the right hand genome or E3 region of PAV 3. However, the claims are broadly drawn to include sites of insertion of heterologous DNA at any point in the adenovirus including the E I and E4 regions.
>
> The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.
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> The instant specification provides the information regarding the PAV-3 tri-partite leader sequences which are different in size and location to the human adenoviruses. The 37 C.F.R. 1.132 declaration of Jeffrey Hammond (Paper No. 24) indicated that for successful production of porcine adenovirus expressing a heterologous gene (1) knowledge of the structure of the tri-partite leader and major late promoter is required (2) and there is the requirement for processing through primary pig kidney cells. The declaration indicates that it is necessary to have an understanding of the structure of the porcine adenovirus in order to determine sequences of the major late promoter and the requisite leader sequences. These sequences where not available in the art at the time of filing. Applicants in their instant specification have provided the necessary structures in order to produce a major late promoter cassette of PAV-3, which they used for the homologues recombination in order to produce porcine adenoviral vector that has a heterologous gene sequence inserted. Neither the specification or the prior art have provide the requisite knowledge regarding the structure of a complete PAV genome or the structure of other PAV genomes, this information would be required if applicants intend to insert heterologous genes into regions other than the PAV region disclosed. In order for homologous recombination to take place the key requirement is the alignment of homologous sequences in two DNA molecules, in the is case these sequences will be present in the wild type virus and they will also need to be present in the shuttle vector providing the heterologous sequence of interest which is to be inserted into the porcine adenovirus. To create the appropriate shuttle vector requires structural knowledge of the region into which the heterologous sequence is to be inserted.
>
> > It must be remembered, however, that"[p]atent protection is granted in return for an enabling disclosure sure of an invention, not for vague intimations of general ideas that mayor may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure." Genentech. Inc. v. Novo Nordisk A/S, 108 F83d 1361, 1365 (Fed. Cir.), cert denied, 522 U.S. 963 (1997) at 1366 (quoting Brenner v. Manson, 383 U.S. 519,536 (1966) (stating, in context of the utility requirement that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"). Thus, while the need for some experimentation is by no means necessarily fatal, "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id.
>
> Thus, the lack of working examples for any other insertion site in the porcine adenovirus, lack of guidance regarding the structure of the porcine adenoviral genome in the specification and the

prior art, and the great breadth of the claims greatly reduces the probability that one of skill in the art would successfully obtain the claimed invention without undue experimentation.

This rejection is respectfully traversed.

Applicants address the issue of whether the enablement requirement is satisfied in connection with the use of primary pig kidney cells. Applicants refer to the preceding discussion regarding such use and respectfully assert again that the claim scope should not be limited to a preferred embodiment. One skilled in the art conducting routine experimentation could test another range of pig cell lines, as was noted in the First Declaration, to determine whether recombinants can be generated with the same, less, or more efficiency. Applicants demonstrate that the teaching of the disclosure enabled one skilled in the art to make or use the claimed invention.

Multiple factors support the satisfaction of the enablement requirement. Here, a substantial amount of direction or guidance was presented in the specification. Structural and sequence information was disclosed in the instant application. Complete restriction maps were provided. Not only were recombinant vectors constructed, but significant clinical results were achieved. As noted, working examples were provided in the specification; this disclosure is bolstered by the partial sequence information that was public knowledge at the time of filing.

Another factor relevant to enablement is the existence of other knowledge in the art. Dr. Hammond in his Second Declaration addresses the status of knowledge in the art at the filing date of the structure of a complete PAV genome or of other PAV genomes. He attests that previous partial sequence knowledge in combination with the teaching of the specification would have allowed the skilled person to insert a heterologous sequence into the right hand end as defined (50 to 100 map units). Importantly, knowledge of the structure of a complete PAV genome would not have been required to successfully insert foreign genes into regions other than the PAV regions disclosed.

Applicants thus demonstrate that by virtue of the direction provided in the specification, other available knowledge, and the working examples, those of ordinary skill in the art could understand and carry out the invention as claimed without undue experimentation.

Request for Reconsideration and Withdrawal of the Rejections

In connection with this reply, Applicant respectfully requests reconsideration and withdrawal of the rejections in the examination of this application.

Reason for Amendments

Amendments to the claims herein are not made for purposes of patentability but are made to clarify the subject matter of the present invention. Applicants believe that the claims without the present amendments are patentable in light of this Response, previous Responses, and accompanying Declarations. Applicants specifically do not surrender any scope possibly available under the doctrine of equivalents.

Allowability of the present claims

Applicants have made a valuable contribution the art in the form of an important, useful, and pioneering invention. For example, by supplying the promoter and leader sequences, Applicants have provided the art with an adequate written description and sufficient enablement to insert and express heterologous DNA sequences into a wide range of sites in any porcine adenovirus. The written description in the as-filed application along with knowledge available at the relevant priority filing date and the satisfaction of the enablement requirement support the breadth of the claimed invention.

Conclusion and Request for Rejoinder

This application appearing to be in condition for allowance, passage to issuance and a timely Notice of Allowance is respectfully requested. Rejoinder and allowance of withdrawn claims, claims 45-50 and 52-62 which were withdrawn from consideration is respectfully requested in view of the allowability of the linking claims.

This Amendment is accompanied by a Request for Extension of Time as necessary and a check in the amount of $950 for such Extension. It is believed that an extension of three months is necessary. For any Extension or for any other required fee, please charge any deficiency or credit any overpayment to Deposit Account 07-1969.

Respectfully submitted,

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Attorney docket No. 2-00
can: February 27, 2004